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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,558	10/15/2003	Glen S. Kwon	33-02	7151

23713 7590 03/25/2008

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
03/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,558	KWON, GLEN S.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 2-25-08 is acknowledged.

Claims included in the prosecution are 1-16.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onyuksel et al (6,217,886) of record.

Onyuksel et al disclose a method of preparation of micelles containing polyene compounds, Amphotericin B and Nystatin. The method involves dissolving the water insoluble compound and the lipid conjugated to a Water-soluble polymer (PEG-DSPE) in an organic solvent, removal of the organic solvent and hydrating the lipid film to form micelles (col. 14, lines 15-47; claims 7-11 and 31). The composition further includes a cryopreservative (col. 14, line 67). What are lacking in Onyuksel et al are the pressure and temperature conditions under which the organic solvent is removed from the PEG-DSPE, active agent solution before hydrating it. However, in the absence of showing unexpected results, evaporation of a solvent is a manipulatable parameter in the highly developed chemical sciences. The examiner also points out that Onyuksel et al in Example 1 teach the use of rotoevaporator to remove the solvent. Since

rotoevaporation is done under vacuum conditions, the pressure is lower than the atmospheric pressure even possibly including the claimed pressures. Onyuksel et al also lacks the teachings of the ratios of PEG-DSPE to amphotericin B. In the examples, Onyuksel et al teach the amounts of the active agent in terms of weight and not moles. In the absence of showing the criticality, it is deemed obvious to manipulate the basic teachings of Onyuksel et al to obtain micelles with the desired amounts of the active agents. Finally it should be pointed out that Onyuksel et al specifically disclose dextrose as the cryopreservative. However, since dextrose is a sugar and sugars are known cryopreservatives, one of ordinary skill in the art at the time the invention was made would expect reasonable expectation of success using dextrose.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Onyuksel reference teaches the dissolution of PEG-DSPE in an organic solvent, drying to prepare micelles and then after hydration, the hydrated micelle containing material is mixed with the biologically active agent. The examiner disagrees. The teachings of Onyuksel on col. 14, clearly indicate the mixing of the biologically active agent and lipids in a solvent. Applicant once again argues that Onyuksel does not disclose that a polyene antibiotic-containing antibiotic preparation (made by the method of Onyuksel) would contain deaggregated antibiotic (for example, Am B). According to applicant the present invention relies on deaggregated Am B as a means for minimizing hemolytic activity while providing a soluble formulation of this difficult-to- administer therapeutic agent and that the presently claimed preparation process allows for the association of the polyene antibiotic with PEG-DSPE in a way

which prevents aggregation of antibiotic when hydrated, thus minimizing its toxicity (as measured by hemolysis). Further according to applicant, the cited Onyuksel actually teaches away from the present claimed method for providing a polyene antibiotic formulation which is soluble and has reduced toxicity (due to deaggregated state) as compared to known prior art compositions, either with respect to the polymer carrier or aggregated polyene antibiotic. These arguments are not persuasive. Claims 7-9 in Onyuksel teach the same method of preparation of the composition containing the biologically active agent and the compounds taught by Onyuksel are amphotericin B and Nystatin and therefore, one would expect similar product and applicant has not shown that amphotericin B in Onyuksel is not in s deaggregated form. Applicant argues that Onyuksel does not teach instant conditions of hydration. The examiner points out these are manipulatable parameters practiced by an artisan. Applicant argues that Onyuksel teaches a crystalline product or a sterically stabilized micelle preparation and instant invention does not relate to a crystalline product. This argument is not persuasive since as recognized by applicants themselves, Onyuksel teaches both crystalline and micellar products (hydrated). Claim 9 in Onyuksel clearly indicates micellar formation. Applicant's arguments that Onyuksel teaches a molar ratio of polymers to bioactive molecule of 125: 1 and 250:1 and in examples 4, 5 and 7 a ratio of 50: 1. These arguments are not persuasive since claim 1 does not recite any ratios at all. Furthermore, in example 1, Onyuksel teaches the criticality of maintaining the critical micellar concentrations of PEG-DSPE and therefore, it would have been obvious to one of ordinary skill in the art to vary the amounts of the active agent, which depends upon

several factors such as the age of the patient, severity of the diseases and others, but maintain the amounts of the PEG-DSPE within the micellar levels. With regard to applicant's arguments that in Example 12, Onyuksel teaches detergents, the examiner points out that instant claim language does not exclude the presence of these compounds.

3. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen et al (US 2004/0013717) by itself or in view of Yu et al (Journal of Controlled Release, 1998) of record or vice versa.

Allen et al disclose micellar formulations containing PEG-DSPE to deliver any chemically or biologically active agent. The method of preparation involves dissolving the active agent and the phospholipid in an organic solvent, evaporation of the organic solvent using a rotary evaporator increasing the vacuum in increments of 25 mbar and hydrating the lipid film to form the micelles. The composition can be freeze-dried in the presence of a cryoprotectant such as a saccharide and rehydrated before use. The molecular weight of PEG is between 1000-10,000. (0016-0018, 0025, 0028, 0030, 0035, 0087, Examples 1 and 2). Although Allen et al do not specifically teach that the active agent to be amphotericin B, it would have been obvious to one of ordinary skill in the art to use any active agent including amphotericin B with a reasonable expectation of success since Allen et al teach its general applicability and provide guidance.

Yu et al teach polymeric micelles for the delivery of amphotericin. The polymer used for the formation of micelles is a PEG derivative of aspartic acid. According to Yu,

the use of the polymeric micelles reduces the haemolytic activity of amphotericin B (abstract).

One of ordinary skill in the art would be motivated to use amphotericin B as an active agent in the micelles of Allen et al with a reasonable expectation of success since the reference of Yu et al shows the knowledge in the art of encapsulation of PEG containing polymeric micelles for the reduction of haemolytic activity of amphotericin B. Alternately, the use of PEG-DSPE instead of PEG-asp in the micelles of Yu et al would have been obvious to one of ordinary skill in the art since the reference of Allen et al shows that PEG-DSPE also forms micelles and such micelles could be used for the delivery of active agents. Although Allen et al do not specifically teach dextrose as the saccharide, the use of any saccharide would have been obvious to one of ordinary skill in the art with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that Allen focuses on photosensitizers and suggests the use of any chemically or biologically active agent and that this represents a vastly broad class of molecules, of which the polyene antibiotics are a small class. This argument is not persuasive since as recognized by applicants themselves, Allen is suggestive of the use any active agent and therefore, it is within the skill of the art to use any active agent including polyene antibiotics with a reasonable expectation of success (see also Supreme court decision in KSR International Co. V. Teleflex Inc., 550 U.S. -, 82 USPQ2d 1385 (2007).

Applicant argues that Yu provides an alternative strategy to that claimed for formulating Am B. According to applicant, Yu teaches a different polymeric material and teaches a different method and that there is no indication that various components such as the polymer are interchangeable. This argument is not persuasive since Yu shows the knowledge in the art of encapsulating Am B in micellar formulations that too with a polymer containing micelles. Therefore, one of ordinary skill in the art would be motivated to use the micelles of Allen to encapsulate Am B. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

4. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Onyuksel et al (6,217,886). OR Allen et al (US 2004/0013717) by itself or in view of Yu et al (Journal of Controlled Release, 1998) of record or vice versa as set forth above, further in view of McShane (6,906,042).

The teachings of Onyuksel et al, Allen et al, Yu et al have been discusses above. What is lacking in these references is the teaching of the use of dextrose.

McShane while disclosing micellar formulations teaches that lyophilized micellar preparations can be rehydrated with dextrose solution, which is suitable for intravenous administrations (col. 12, lines 15-23). The use of dextrose in the micellar compositions of Onyuksel et al, Allen et al and Yu et al would have been obvious to one of ordinary skill in the art since such a micellar preparation is suitable for intravenous administration as taught by McShane.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that McShane appears to relate to micelles having a very specific compound of the formula A and apart from the common use of the term, 'micelles' and the mention of dextrose, the disclosure of McShane is not relevant to the patentability of the presently claimed invention. This argument is not persuasive since McShane teaches the advantage of lyophilizing the micellar composition and the use of cryopreservatives; the advantage being to be able to dilute and prepare a solution suitable for intravenous administration. This advantage would be the same irrespective of what compound is used in the micelles and applicant has not shown any unexpected results by using dextrose in the compositions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK